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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,181	04/26/1999	LAURENT BRACCO	ST96030-US	9384

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WILEY, REIN & FIELDING, LLP
ATTN: PATENT ADMINISTRATION
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EXAMINER
KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,181	BRACCO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-60* is/are pending in the application.

4a) Of the above claim(s) *56-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *26 April 1999* is: a)☐ approved b)☒ disapproved by the Examiner.*

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)*
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 12/23/02 has been acknowledged.

Claims 55-60 are pending.
Claims 55 and 60 are examined in this office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim,* ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 55 and 60) in Paper No. 24 is acknowledged. The traversal is on the ground(s) that subject matte of two group-I and group-II is related and there is no serious burden to examine these groups as one single invention. This is not found persuasive because inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case nucleic acid and antibody are structurally and functionally different compounds. These products can be used in a materially different process. For example, antibodies can be use to label cell surfaces whereas DNA can be used as nucleic acid probes. In addition, searching of one group would not fully anticipate the

subject matter of other group and therefore would require additional search. For example, search of a polynucleotide sequence is not required for the search of 11D3 antibody. Therefore there is serious search burden to examine all the groups is one single

The requirement is still deemed proper and is therefore made FINAL.

Claims 56-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 24.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The substitute oath or declaration filed on 09/23/02 is defective because:

It does not identify the foreign application for patent or inventor's certificate on which priority is claimed pursuant to 37 CFR 1.55, and any foreign application having a filing date before that of the application on which priority is claimed, by specifying the application number, country, day, month and year of its filing.

It was not executed in accordance with either 37 CFR 1.66 or 1.68.

In addition, the specification to which the oath or declaration is directed has not been adequately identified in the original oath, which is not in agreement with the declaration as filed on 09/23/02.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claim 55 and 60 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a non-statutory subject matter. The invention as claimed encompasses a product that does not require the hand of man. Changing "antibody" to – isolated antibody – or – purified antibody – would over come this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 50 and 60 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention:

Invention relates to the 11D3 antibody that recognizes an epitope on p53 protein.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses any and all variant of the antibody 11D3, which recognizes any and all epitopes on a p53 protein (on any and all variants of p53 protein, e.g. wild type or mutant p53). At best the specification as filed only disclosed a single variant of antibody 11D3 encoded by SEQ ID NO:3 (spec. page 29, lines 1-9). The specification fails define any epitope specificity on p53 (wild-type p53 or any and all p53 mutants), to which the antibody 11D3 binds explicitly or implicitly. At best the specification teaches that the antibody 11D3 causes retardation of wild type p53 and His273-p53 mutant in a gel mobility assay (spec page 29, line 1-9).

State Of Art And Predictability:

The art at the time of filing define epitopes as a region on an antigen molecule to which antibody or the T cell receptor binds specifically. Antibodies binds in a more or less exact three-dimensional fit within an epitope. This structure may be formed from residues on different regions of protein antigen molecules, which in the native state are closely apposed due to protein folding. Thus the 3-dimensional structure of the protein molecule is considered essential. Epitopes recognized by T cells are peptide fragments processed by APCs. Since a continuous primary sequence is necessary for T cell recognition but not for antibody recognition, the epitopes recognized on the same protein molecule by each (antibody or T-cell) are different. In this regard, the specification fails to provide sufficient guidance and objective evidence as to the linear or three-dimensional conformation of the p53 polypeptide, which may or may not

constitute a epitope (see Herbert et al. The Dictionary of Immunology, Academic Press, 4th edition, 1995). Moreover, defining epitopes is not as easy as it seems. Even when the epitope is defined in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (Greenspan et al, Nature Biotechnology 7:936-937 (1999) see page 937, 2 column). Furthermore, the state of art teaches that mutation in p53 produces conformational changes that affect antibody specificities. The binding of a p53 mAb to a specific epitope not only varies with the mutations in p53 but also depends upon epitope variation found among different animal species (Legros et al Oncogene 9:3689-3694, 1994, see page 3690, table 1; page 3692, table-2 and page 3693, fig-6). Furthermore, Fromentel et al teaches that 11D3 epitope only maps to the p53 carboxy-terminal domain (by p53 deletion analysis) but fall short of clearly defining any p53 specific epitope (Fromentel et al Oncogene 18:551-557, 1999). In instant case the specificity of 11D3 has not been defined and the specification fails to provide any guidance how to characterize the 11D3 in terms of epitope specificity.

Quantity Of Experimentation Required:

Considering the state of art and the limited guidance provided in the specification one skill in the art would have to engage in excessive and undue amount of experimentation to characterize any and all variants of the antibody 11D3 especially in view of any and all p53 related epitope. In instant case defining an epitope for any and all variants of an antibody like 11D3 is not considered routine in the art and without sufficient guidance to 11D3 specific epitope the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is

noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). In addition, considering the lack of disclosure regarding the availability of the antibody 11D3 through a biological deposit, it is unclear how one skill in the art would use the product as claimed (see MPEP 2400 and deposit requirements below). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Deposit Requirement

Applicant's referral to the antibody 11D3 on page 29 of the specification is insufficient assurance that all of the conditions of 37 CFR 1.801-1.809 have been met.

If the deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by Applicant, Assignee, or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is required. This requirement is necessary when a deposit is made under the provisions of the Budapest Treaty, as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and address of the depository is required.

Furthermore, unless deposit was made at or before the time of filing, a declaration filed under 37 CFR 1.132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited material by its depository accession number, establish that the deposited material is the same as that described in the specification, and establish that the deposited material was in Applicant's possession at the time of filing. See In re Lundak, 27 USPQ 90.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request, or for the enforceable life of the patent, whichever is longer;
d) a test of the viability of the biological material at the time of the deposit was made, and that the test results indicated that said biological material was viable (see 37 CFR 1.807); and,
e) the deposit will be replaced it should ever become inviable.

5. Claims 55 and 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention**.

The scope of invention as claimed encompasses any and all variant of the antibody 11D3 recognizing any and all epitopes on a p53 protein (on any and all variants of p53 protein). At best the instant specification as filed only disclosed one variant of antibody 11D3, which recognized p53 mutant His273 (spec. page 29, lines 1-10). The specification even fails define an epitope on p53 (wild-type p53 or any and all p53 mutants), which the antibody 11D3 recognizes explicitly or implicitly.

The art at the time of filing define epitopes as a region on an antigen molecule to which antibody or the T cell receptor binds specifically. Antibodies binds in a more or less exact three-dimensional fit within an epitope. This structure may be formed from residues on different regions of protein antigen molecules, which in the native state are closely apposed due to protein folding. Thus the 3-dimensional structure of the protein molecule is considered essential. Epitopes recognized by T cells are peptide fragments processed by APCs. Since a continuous primary sequence is necessary for T cell recognition but not for antibody recognition, the epitopes recognized on the same protein molecule by each (antibody or T-cell) are different. In this regard, the specification fails to provide sufficient guidance and objective evidence as to the linear or three-dimensional conformation of the p53 polypeptide, which may or may not constitute a epitope (see Herbert et al. The Dictionary of Immunology, Academic Press, 4th edition, 1995). Moreover, defining epitopes is not as easy as it seems. Even when the epitope is defined in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (Greenspan et al, Nature Biotechnology 7:936-937 (1999) see page 937, 2 column). Furthermore, the state of art teaches that mutation in p53 produces conformational changes that affect antibody specificities. The binding of a p53 mAb to a specific epitope not only varies with the mutation in p53 but also with epitope variation among different animal species (Legros et al Oncogene 9:3689-3694, 1994, see page 3690, table 1; page 3692, table-2 and page 3693, fig-6). Furthermore, Fromentel et al teaches that 11D3 epitope only maps to the p53 carboxy-terminal domain by p53 deletion analysis but fall short of clearly defining any p53 specific epitope (Fromentel et al Oncogene 18:551-557, 1999). In instant case

the specificity of 11D3 is not defined and the specification fails to provide any guidance how to characterize the 11D3 in terms of epitope specificity. Thus considering the applicant's disclosure it is unclear how one skill in the art would identify any variant of 11D3 that binds to the same epitope without knowing the 11D3 epitope specificity.

At best the instant specification only disclosed antibody 11D3 and fails to teach any variant thereof by any structural and functional limitations. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In addition possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In the instant case the antibody 11D3 has been defined only by a statement of function (*binds to same epitope, wherein the epitope has not been defined*), which conveyed no distinguishing information about the identity of the claimed antibody, such as its relevant structural or physical characteristics of epitopes recognized. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 55 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 is indefinite because it is unclear what is "the same epitope" in this context. It is unclear whether the limitation "the same epitope" is defined in view of the 11D3 antibody or a variant thereof.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

SUMESH KAUSHAL
PATENT EXAMINER